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Being Prepared
Emergency Treatment Following a Nerve Agent Release

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ABSTRACT
Nerve agents are extremely toxic and are some of the most lethal substances on earth. This group of chemicals consists of sarin, cyclosarin, soman, tabun, VX, and VR. It is currently unknown how many countries possess these chemicals and in what quantities. These agents work through altering the transmission and breakdown of acetylcholine by binding to, and inactivating, acetylcholinesterase. This results in an uncontrolled and overwhelming stimulation of both muscarinic and nicotinic receptors. Receptor activation at these sites can lead to a wide variety of clinical symptoms, with death frequently resulting from pulmonary edema. Antidotal therapy in this setting largely consists of atropine, pralidoxime, and benzodiazepines, all of which must be administered emergently to limit the progression of symptoms and prevent the enzyme inactivation from becoming permanent. This article reviews the mechanism of action of the nerve agents and their effects on the human body, the currently available therapies to mitigate their impact, and important therapeutic considerations for health care practitioners in the emergency department. **Key words:** atropine, cholinergic crisis, nerve agent, organophosphate, pralidoxime

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NERVE AGENTS are extremely toxic and are some of the most lethal substances on earth. They are chemically related to organophosphate insecticides and were originally developed for a similar purpose. However, following their development in the 1930s, these agents were immediately recognized as possessing significant potential for use by the German military in chemical warfare (Barthold & Schier, 2005). They were subsequently weaponized,

mass-produced, and stockpiled by Nazi Germany. However, they were never actually deployed during World War II. It was not until the 1980s that sarin and tabun were used in the Iran–Iraq war, contributing to 100,000 Iranian casualties (Barthold & Schier, 2005). In the 1990s, a terrorist group by the name of Aum Shinrikyo used sarin in two separate attacks in Japan, which killed 19 people and caused more than 5,000 others to seek medical care (Okudera, 2002; Okumura et al., 1996). Although many nations have since destroyed the majority of their stockpiles of nerve agents as a part of an international treaty regarding chemical weapons, it is currently unknown how many countries possess these agents and in what quantities (Barthold & Schier, 2005). Therefore, it is important for all emergency department (ED) practitioners to be knowledgeable about these agents' mechanism of action, clinical impact, and existing countermeasures.

BACKGROUND AND PATHOPHYSIOLOGY

Nerve agents and organophosphate insecticides act through modulating the transmission and breakdown of acetylcholine (Sidell & Borak, 1992). There are two main categories of nerve agents that exist: the G agents and the V agents (see Table 1). The category of G agents are termed this as they were discovered in Germany whereas the category V agents are named for their high potency and ability to penetrate the skin, much like "venom" (Newmark, 2004). Classifying the substances as either G or V agents serves to differentiate them on the basis of unique physical and chemical characteristics. For example, G agents tend to be colorless in their pure form, whereas V agents possess an amber color. All liquid nerve agents are volatile and can evaporate at room temperature, but V agents tend to be far more persistent and less volatile than G agents. The persistence and volatility of nerve agents is important to consider in a terrorist event. Agents, such as those in the V category, that are less volatile will be present in the environment for a longer period of time because they are heavier than air and tend to settle to ground level. This decreases the incidence of inhalation exposure and increases the risk of exposure from ground contamination. Therefore, G agents represent chemicals that are far more likely to result in a high number of inhalation exposures following a terrorist release, whereas V agents are far more challenging to disseminate but have a higher risk of delayed transdermal exposure following a terrorist event. Although organophosphate insecticides are relatively easy to acquire and could be potentially used in a terrorist attack, they are typically far more dilute, challenging to disseminate, and require a far higher dose to cause human harm.

Table 1. Nerve agents

G agents	V agents
Sarin (GB)	VX
Cyclosarin (GF)	VR
Soman (GD)	
Tabun (GA)	

Acetylcholine acts as the regulating neurotransmitter in two different classes of receptors, the muscarinic and the nicotinic receptors (Sidell & Borak, 1992). These receptors are located in the sympathetic and parasympathetic nervous system, the central nervous system, and skeletal muscles. In normal nervous system transmission, an action potential is conducted down a neuron to the axonal terminus where there is a release of neurotransmitter molecules, such as acetylcholine (see Figure 1). These chemicals then cross the neuromuscular junction that separates the two neurons. The binding of neurotransmitters to the postsynaptic receptor creates an action potential leading to muscle contraction. After acetylcholine disassociates from the postsynaptic receptor, it is then hydrolyzed and inactivated by acetylcholinesterase. Any blockade of this enzyme will, therefore,

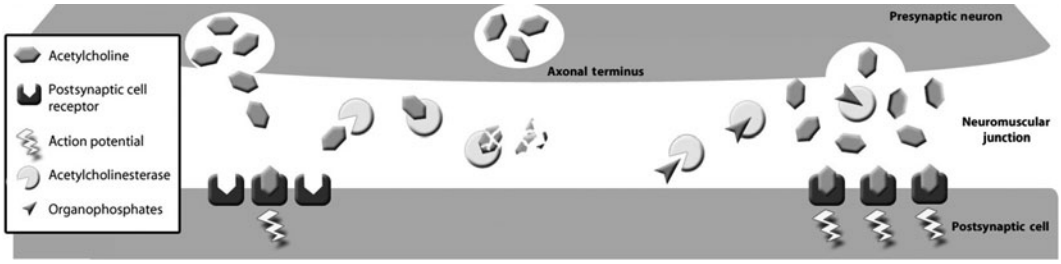

Figure 1. Nerve agent mechanism of action. During nerve signal transmission, acetylcholine is released from the axonal terminus into the neuromuscular junction. After acetylcholine crosses the neuromuscular junction, it binds to the postsynaptic cell receptor and an action potential is generated. After acetylcholine has transmitted the intended signal, it disassociates from the postsynaptic receptor and is hydrolyzed and inactivated by acetylcholinesterase. Organophosphates bind to acetylcholinesterase and inactivate these enzymes. This results in overwhelming signal transmission by acetylcholine.

result in an uncontrolled and overwhelming amount of acetylcholine available for transmission.

Nerve agents bind at the active site of acetylcholinesterase, inactivating the functional capabilities of the enzyme (Sidell & Borak, 1992). This results in accumulation of acetylcholine in the neurosynaptic cleft. Initially, this bond is reversible; however, it can undergo a time-dependent process known as "aging" in which the enzyme is permanently inhibited (Mason, Waine, Stevenson, & Wilson, 1993; Masson & Goasdoue, 1986). The time required for this process can vary depending on the specific nerve agent but ranges from hours to days. This is yet another difference that exists between nerve agents and insecticides, in that the latter do not undergo aging, and their activity is always reversible.

CLINICAL PRESENTATION

Exposure to nerve agents is most likely to occur through dermal or inhalational routes, although ingestion is also possible (Collombet, 2011; Newmark, 2004). Initial symptoms will vary depending on the route of exposure. However, regardless of the route of exposure, similar clinical presentations will eventually result. Compared with inhalational exposure, dermal exposure is particularly dangerous, as nerve agents are not directly irritating to the skin, thus going unnoticed, and usually result in delayed systemic symptoms. In addition, the sequence of symptoms in dermal exposure may also be different compared with inhalational exposure. For example, encountering nerve agent vapor will likely result initially in miosis, rhinorrhea, and salivation within a few minutes as those cholinergic synapses are exposed externally (Anderson, 2012). Dermal exposure, on the contrary, will initially result in localized sweating, followed by muscle fasciculations. In both scenarios, however, depending on the level of contamination, the inhibition of acetylcholinesterase leads to significant symptomatology.

Unchecked muscarinic receptor activation results in symptoms that are typically remembered by the mnemonic DUMBELS: diaphoresis and diarrhea, urination, miosis, bronchorrhea and bronchospasm, emesis, lacrimation, salivation and secretion (Grob & Harvey, 1958; Namba, Nolte, Jackrel, & Grob, 1971). Of these, miosis tends to be the most frequent (Okudera, 2002). Respiratory system dysfunction, highlighted by bronchorrhea and bronchoconstriction, can result in life-threatening pulmonary edema and is the leading cause of death from nerve agents (Rickett, Glenn, & Beers, 1986). The result of overstimulation of nicotinic receptors also leads to the symptoms of mydriasis, muscle fasciculations, generalized muscle cramps, pallor, flaccid paralysis, hypertension, and

tachycardia (Grob & Harvey, 1958; Namba et al., 1971). The cardiovascular system can respond in a number of unpredictable ways following exposure (Namba et al., 1971). Bradycardia, tachycardia, and normal heart rates have been known to occur as well as hyper- and hypotension. The central nervous system can be significantly impacted by exposure and result in central respiratory depression, seizures, and coma. Regardless of whether presenting symptoms result from dermal or inhalational absorption, the key determinant of symptomatology is the degree of exposure. Minimal exposures will likely result in local eye irritation, miosis, rhinorrhea, diaphoresis, or muscle fasciculations at the site of contact. Large exposures can result in severe symptoms, including respiratory dysfunction and death. Dermal exposures also carry with them an inherent risk of prolonged symptomatology because of a depot effect of the agent on the skin (Newmark, 2004).

Following the acute cholinergic effects of nerve agent exposure, a poorly understood syndrome known as "intermediate syndrome" can develop and can be a significant cause of morbidity (Senanayake & Karalliedde, 1987; Sudakin, Mullins, Horowitz, Abshier, & Letzig, 2000). The symptoms of this syndrome include cranial nerve weakness, proximal muscle weakness, and respiratory failure. It is speculated to be secondary to neuronal dysfunction as a result of sustained acetylcholinesterase inhibition (Abdollahi & Karami-Mohajeri, 2012). The debate surrounding this syndrome is centered on the fact that many contend that it is an extension of the acute symptomatology rather than a distinct syndrome. Still, others suggest that this is the result of potentially delayed absorption or accumulation of the nerve agent. This lack of consensus is reflected in the wide range of the estimated incidence of intermediate syndrome (5%–65%). The onset of this syndrome seems to occur 1–3 days after the acute crisis and recovery occurs between 5 and 18 days after the onset of symptoms. Unfortunately, no therapy has been identified as being beneficial in this situation. Nevertheless, it is important for practitioners to remain vigilant in their clinical monitoring of patients beyond the initial resolution of acute poisoning, as intermediate syndrome can lead to late-onset respiratory failure and death (Abdollahi & Karami-Mohajeri, 2012).

Another well-documented delayed impact of organophosphate exposure is organophosphate-induced delayed neurotoxicity (polyneuropathy; Mutch, Blain, & Williams, 1992). This is theorized to be the result of the nerve agent's activity on a protein called "neurotoxic esterase" that also undergoes phosphorylation and aging much like acetylcholinesterase. Symptoms of this polyneuropathy tend to develop 1–4 weeks after exposure and consist of muscle pains and weakness in the lower extremities, followed by paralysis. The upper extremities can also be involved in severe cases. Currently, no treatment of this condition exists beyond standard supportive care and over time, some patients may regain some function.

ANTIDOTAL THERAPY

After decontamination measures are complete, the first antidotal priority in the event of a nerve agent exposure is the abatement of bronchorrhea because it is the leading cause of death (Sidell & Borak, 1992). The process of reactivating acetylcholinesterase before aging occurs should begin shortly thereafter. The two primary agents utilized to address these priorities are atropine and pralidoxime (2-PAM). Atropine's primary role in this setting is its efficacy as an antimuscarinic rather than its traditional use as a vagolytic. As an antimuscarinic, it competes with acetylcholine for the postsynaptic muscarinic receptors, thus dampening the clinical effects of excess acetylcholine caused by the nerve agent. This deviation from its traditional use is most clearly seen in the recommended dosing of this agent (see Tables 2 and 3), which is much higher than its dosing in the setting of bradycardia (Agency for Toxic Substances and Disease Registry, 2011). Although the Centers for Disease Control

Table 2. Recommendations for nerve agent therapy—prehospital management

Patient's age	Antidotes[a]		Other treatment
	Mild/moderate symptoms[b]	Severe symptoms[c]	
Infant (0–2 years)	Atropine: 0.05 mg/kg IM; 2-PAM Cl: 15 mg/kg IM	Atropine: 0.1 mg/kg IM; 2-PAM Cl: 25 mg/kg IM	**Assisted ventilation** should be started after administration of antidotes for severe exposures.
Child (2–10 years)	Atropine: 1 mg IM; 2-PAM Cl: 15 mg/kg IM	Atropine: 2 mg IM; 2-PAM Cl: 25 mg/kg IM	
Adolescent (older than 10 years)	Atropine: 2 mg IM; 2-PAM Cl: 15 mg/kg IM	Atropine: 4 mg IM; 2-PAM Cl: 25 mg/kg IM	**Repeat atropine (2 mg IM)** at 5- to 10-min intervals until secretions have diminished and breathing is comfortable or airway resistance has returned to near normal.
Adult	Atropine: 2–4 mg IM; 2-PAM Cl: 600 mg IM	Atropine: 6 mg IM; 2-PAM Cl: 1800 mg IM	
Elderly, frail	Atropine: 1 mg IM; 2-PAM Cl: 10 mg/kg IM	Atropine: 2–4 mg IM; 2-PAM Cl: 25 mg/kg IM	

Note. IM = intramuscular.

[a]2-PAM Cl solution needs to be prepared from the ampule containing 1 g of desiccated 2-PAM Cl: inject 3 ml of saline, 5% distilled or sterile water into ampule and shake well. Resulting solution is 3.3 ml of 300 mg/ml.

[b]Mild/moderate symptoms include localized sweating, muscle fasciculations, nausea, vomiting, weakness, and dyspnea.

[c]Severe symptoms include unconsciousness, convulsions, apnea, and flaccid paralysis.

From "Medical Management Guidelines for Nerve Agents: Tabun (GA); Sarin (GB); Soman (GD); and VX," by Agency for Toxic Substances and Disease Registry, 2011. Retrieved from http://www.atsdr.cdc.gov/MHMI/mmg166.pdf. Reproduced with permission.

and Prevention (CDC) provides clear dosing recommendations, significant variation exists in the literature regarding dosing in this setting (Agency for Toxic Substances and Disease Registry, 2011; Thiermann et al., 2011). The dose of atropine is titrated until secretions are limited and the patient can breathe comfortably without assistance. Once again deviating from the traditional use of this agent, tachycardia is not a contraindication for therapy and exceedingly high doses, or even continuous infusions (0.02–0.08 mg/kg/hr), may be necessary (Dunn & Sidell, 1989). Doses in this range have potential to result in systemic side effects typically not seen in clinical practice when using bolus therapy, such as confusion, pyrexia, ileus, and urinary retention (Eddleston et al., 2004). If these side effects occur, it has been recommended that the infusion be stopped and restarted at 70%–80% of the original dose after symptoms have subsided (Eddleston et al., 2004). Although atropine is the drug of choice in this situation, glycopyrrolate, another antimuscarinic, may also be effective if adequate supplies of atropine are not available. Glycopyrrolate is not approved by the Food and Drug Administration (FDA) for this purpose; however, it has been used to reverse the effects of acetylcholine on muscarinic sites in the setting of carbamate pesticide administration (Bevan, Donati, & Kopman, 1992). Glycopyrrolate does not cross the blood–brain barrier and ideally should not be used alone, without atropine, but it may have some utility in treating specific peripheral muscarinic symptoms (Barthold & Schier, 2005; Bird, Gaspari, & Dickson, 2003).

Despite atropine's efficacy at alleviating muscarinic symptoms, it is ineffective in resolving the nicotinic symptoms associated with nerve agent exposure or preventing aging. Pyridinium oximes, such as pralidoxime, are effective in reversing both

Table 3. Recommendations for nerve agent therapy—emergency department management

Patient age	Antidotes[a]		Other treatment
	Mild/moderate symptoms[b]	Severe symptoms[c]	
Infant (0–2 years)	Atropine: 0.05 mg/kg IM; 2-PAM Cl: 15 mg/kg IV slowly	Atropine: 0.1 mg/kg IM; 2-PAM Cl: 15 mg/kg IV slowly	**Assisted ventilation** as needed. **Repeat atropine (2 mg IM or 1 mg IM for infants)** at 5- to 10-min intervals until secretions have diminished and breathing is comfortable or airway resistance has returned to near normal.
Child (2–10 years)	Atropine: 1 mg IM; 2-PAM Cl: 15 mg/kg IV slowly	Atropine: 2 mg IM; 2-PAM Cl: 15 mg/kg IV slowly	
Adolescent (older than 10 years)	Atropine: 2 mg IM; 2-PAM Cl: 15 mg/kg IV slowly	Atropine: 4 mg IM; 2-PAM Cl: 15 mg/kg IV slowly	
Adult	Atropine: 2–4 mg IM; 2-PAM Cl: 15 mg/kg (1g) IV slowly	Atropine: 6 mg IM; 2-PAM Cl: 15 mg/kg (1g) IV slowly	**Phentolamine** for 2-PAM induced hypertension (5 mg IV for adults; 1 mg IV for children). **Diazepam** for convulsions: (0.1–0.5 mg IV for infants to 5 years; 1 mg IV for children older than 5 years; 5 mg IV for adults)
Elderly, frail	Atropine: 1 mg IM; 2-PAM Cl: 5–10 mg/kg IV slowly	Atropine: 2–4 mg IM; 2-PAM Cl: 5–10 mg/kg IV slowly	

Note. IM = intramuscular; IV = intravenous.
[a]Mild/moderate symptoms include localized sweating, muscle fasciculations, nausea, vomiting, weakness, and dyspnea.
[b]Severe symptoms include unconsciousness, convulsions, apnea, and flaccid paralysis.
Reproduced from "Medical Management Guidelines for Nerve Agents: Tabun (GA); Sarin (GB); Soman (GD); and VX," by Agency for Toxic Substances and Disease Registry, 2011. Retrieved from http://www.atsdr.cdc.gov/MHMI/mmg166.pdf

muscarinic and nicotinic symptoms provided they are administered prior to enzyme aging (Newmark, 2004). These agents remove the phosphoryl group from the nerve agent-acetylcholinesterase enzyme complex, leading to enzyme reactivation. Although pyridinium oxime does have an ability to function at all acetylcholinesterase sites, it does appear to have a limited ability to cross an intact blood–brain barrier. However, in the setting of seizure activity secondary to severe poisoning, the level of penetration is likely to be elevated (Carpentier, Delamanche, Le Bert, Blanchet, & Bouchaud, 1990; Grange-Messent et al., 1999). The major limitation of this agent is the aging process. If aging occurs prior to pyridinium oxime administration, it is essentially impossible to reactivate it. The aging time period has great variability across different nerve agents, with VX having the longest at 22 days and soman having the shortest at 2 min (Newmark, 2004). As the identification of the actual causative agent may take several hours, pyridinium oximes should be administered in the emergency setting regardless of the potential nerve agent used. Although atropine usage for this indication is fairly standard across the world, oximes can vary by country. In the United States, the monopyridinium oxime pralidoxime (2-PAM) is the agent licensed for use for this indication (see Tables 2 and 3; Agency for Toxic Substances and Disease Registry, 2011; Jokanovic, 2009). Multiple bispyridinium oximes are used elsewhere and include trimedoxime, obidoxime, and asoxime.

Atropine and 2-PAM are both available in a combination autoinjector preparation in the United States (Newmark, 2004). The original design, known as the MARK 1 kit, supplied a dose of 2 mg of atropine and 600 mg of pralidoxime as two separate intramuscular (im) injections (see Figure 2). The newer preparation, known as DuoDote, supplies 2.1 mg of atropine and 600 mg of pralidoxime into one autoinjector (see Figure 3). The loading dose utilized in this setting can be up to 1,800 mg of pralidoxime, or three DuoDotes/MARK 1 Kits, depending on the patient's symptoms. Both preparations still exist throughout the United States in stockpiles, so emergency practitioners need to be familiar with both products. In the setting of a severe nerve agent exposure in a patient in need of intubation, it may be reasonable to administer atropine before attempting the procedure (Newmark, 2004). The termination of bronchospasm and bronchorrhea will greatly facilitate ventilation following intubation. Atropine and pralidoxime may be given intravenously or intramuscularly at the same dosage (Eddleston et al., 2004). Recent animal trials have also demonstrated that intraosseous administration of both atropine and pralidoxime provides rapid and substantial antidote bioavailability (Murray et al., 2012). Although it may be clinically indicated, rapid bolus administration of oximes such as pralidoxime has been associated with side effects including vomiting, tachycardia, hypertension, and cardiac or respiratory arrest (Barthold & Schier, 2005; Eddleston et al., 2004). Therefore, it is recommended that the injection rate not exceed 200 mg/min. These risks must be weighed acutely against the risks of not treating the patient following a life-threatening exposure.

Following initial bolus treatment with atropine and pralidoxime, repeated dosing of each agent may be necessary in severe poisonings if clinically indicated. Additional bolus dosing with atropine is recommended by the CDC and is outlined in Table 3 (Agency for Toxic Substances and Disease Registry, 2011). Guidance regarding supplementary dosing

Figure 2. MARK 1 Kit containing 2 mg of atropine and 600 mg of pralidoxime as two separate intramuscular injectors.

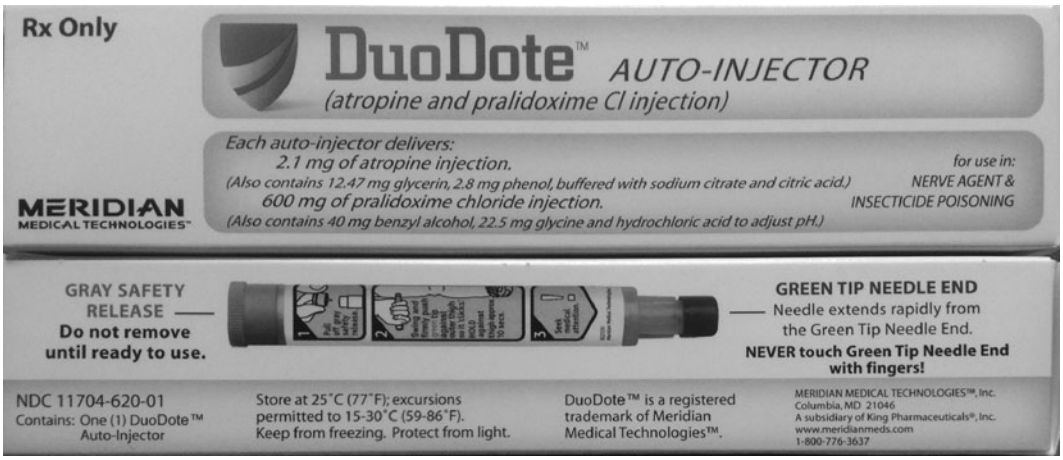

Figure 3. DuoDote injector containing 2.1 mg of atropine and 600 mg of pralidoxime into one intramuscular injector.

with pralidoxime in this situation, however, is far less clear. Some have suggested that a continuous infusion of this agent may provide for a more optimal pharmacokinetic profile and limit side effects associated with bolus infusions (Barthold & Schier, 2005; Eddleston et al., 2004; Medicis, Stork, Howland, Hoffman, & Goldfrank, 1996; Schexnayder, James, Kearns, & Farrar, 1998). If a continuous infusion is implemented, the recommended rates from various studies range from 5–20 mg/kg/hr to 200–500 mg/hr. Limited intravenous (IV) compatibility information is available regarding the use of a continuous infusion and it should, therefore, have a dedicated IV line. If a continuous infusion is not started, reassessment of the patient and consideration for repeated bolus administration with pralidoxime is recommended every 3–8 hr (Barthold & Schier, 2005).

ANTICONVULSIVE THERAPY

The systemic nicotinic and muscarinic stimulation throughout the body caused by nerve agents has wide-ranging implications for various organs, including the brain. The pervasive distribution of cholinergic synapses within the brain will likely result in an initial loss of consciousness, followed by seizure activity (Newmark, 2004). Seizure activity in this setting is thought to be secondary to increased acetylcholine levels and glutamate release. However, some have suggested that it is through the blockade of γ-aminobutyric acid (GABA; Lee, 2003). Nevertheless, the resulting status epilepticus seems to be starkly different from other etiologies, as it is relatively unresponsive to standard antiepileptic therapies such as phenytoin, phenobarbital, or valproic acid (Bajgar, 2004; Lallement et al., 1998; McDonough & Shih, 1997). This is theorized to be due to the wide distribution of the cholinergic system within the brain that renders these agents, that primarily work through limiting the spread of seizure discharges, ineffective. In this setting, benzodiazepines such as diazepam, midazolam, and lorazepam that act through enhancement of GABA activity are the drugs of choice for the treatment of status epilepticus and seizure prevention. Benzodiazepines also have the added benefit of reducing anxiety and muscle fasciculations, which may also assist in patient management. Benzodiazepine therapy is recommended for all patients exhibiting convulsions or in severely poisoned patients (i.e., unconscious, apneic, flaccid paralysis) prior to the development of seizure activity (Jokanovic, 2009). Interestingly, existing

data seem to suggest that atropine may have anticonvulsant properties in this setting, further cementing its role as initial drug therapy (McDonough, McLeod, & Nipwoda, 1987).

PROPHYLAXIS

The aging time of some nerve agents is quite rapid and for soman, in particular, it is about 2 min. Unfortunately, this presents a situation in which there is usually not enough time to administer medication fast enough to prevent aging. As such, a significant amount of effort has gone into looking for prophylactic medications. One agent approved by the FDA for this purpose is pyridostigmine, a medication typically used in the treatment of myasthenia gravis. The prophylactic use of pyridostigmine has been shown to improve survival following soman exposure and was recently used during the Gulf War at a dose of 30 mg every 8 hr to protect troops from possible exposure to nerve agents (Berry & Davies, 1970; Leadbeater, Inns, & Rylands, 1985; Newmark, 2004). Although somewhat counterintuitive, pyridostigmine works to decrease the lethality of soman by reversibly binding to acetylcholinesterase itself, therefore, limiting the number of sites available for soman to irreversibly bind to, and permanently inhibit, the receptors. This subsequently increases the efficacy of pralidoxime when it is administered following exposure. In a domestic terrorist response situation, this agent may have a role in prophylaxing first responders deployed to the affected area. Once exposure to a nerve agent has occurred and it is bound to acetylcholinesterase, pralidoxime has no role and is ineffective. It also has limited ability to cross the blood–brain barrier, so its potential to curb nerve agent phosphorylation of central acetylcholinesterase enzymes is somewhat restricted (Keeler, Hurst, & Dunn, 1991). Pyridostigmine is generally well tolerated, and the most common adverse effects are involved with overstimulation of muscarinic receptors, leading to gastrointestinal disorders, nausea, vomiting, sweating, and increased bronchial secretions (Maggi & Mantegazza, 2011). Large doses have been shown to cause muscle weakness and may stimulate a cholinergic crisis. There have been suggestions that the use of this agent is linked to the development of Gulf War illness as well (Newmark, 2004).

PRACTICAL CONSIDERATIONS

Many lessons were gleaned from the sarin attacks in Japan that ED practitioners should consider in their planning efforts. First of all, ensuring that adequate surge capabilities exist is critical. Because of a lack of coordination between emergency medical services (EMS) and patients who self-transport, a single hospital became rapidly overwhelmed with 640 patients the day of the attack, with many patients bypassing closer hospitals (Okumura et al., 1996). Second, the importance of decontamination cannot be understated. Decontamination is an essential first step in the treatment of patients following such an event to both minimize ongoing exposure to the victims and prevent secondary exposure to medical personnel. In one Japanese hospital following the attacks, several medical personnel in the ED became symptomatic during their treatment of patients and required antidotal therapy (Nozaki et al., 1995). The recommended decontamination method includes showering with soap and water or with 0.5% hypochlorite solution prepared in water (Collombet, 2011). In addition, the mechanism of action of the toxin should be considered when prescribing additional pharmacologic therapies. Because of bronchorrhea and bronchoconstriction, rapid sequence intubation may be necessary in certain patients. The use of a nondepolarizing neuromuscular blocker would be strongly recommended in this setting over succinylcholine, a depolarizing neuromuscular blocker. Because succinylcholine is metabolized by plasma cholinesterases, inhibition of these enzymes by nerve agents may lead to prolonged paralysis and untoward outcomes (Selden & Curry, 1987; Sener, Ustun, Kocamanoglu, & Tur, 2002).

Institutions should develop computerized provider order entry order sets and electronic medication administration records for nerve agent exposure in advance. The emergent use of medications and dosages that are not routinely used in the ED provides for the perfect scenario for medication errors. The development of these order sets will allow for more seamless use of these agents, minimize confusion, and assist in supporting consistent documentation in such a chaotic event.

Recognizing the urgency of antidotal therapy in this scenario, in 2004, the CDC established a voluntary participation project called "CHEMPACK" (Levinson, 2009). This program was developed to ensure the forward placement of nerve agent antidotes in numerous locations in the United States. The intent is that the antidotal therapies would be immediately accessible for use by emergency providers (Levinson, 2009). These are large wire cages kept in secure locations that contain atropine, pralidoxime, and diazepam in various forms. There are two types of these cages: Emergency medical services containers and hospital containers. These titles describe the contents of the containers rather than their location, as EMS containers are located inside many hospitals in the United States. The EMS containers have more autoinjectors whereas the hospital containers are stocked with more multidose vials. As such, the EMS containers have enough antidote to treat approximately 454 patients, whereas the hospital containers are able to treat around 1,000 patients. These containers are owned and maintained by the CDC and are intended for use only in the event of a chemical agent release. Health care practitioners should contact their state and local health departments regarding CHEMPACK locations in their area and inquire about the emergency plans that have been developed regarding their use in an event.

CONCLUSION

Nerve agents are lethal chemicals that can inflict substantial morbidity and mortality if dispersed in a highly populated area. Their mechanism of action is complex, and limited information is available regarding the long-term effects of these agents on survivors. Although antidotes do exist for these agents, their efficacy is largely predicated on the speed with which they are administered to the affected population. Therefore, the CDC has developed a program to predeploy stockpiles of antidotes in strategic areas to expedite patient treatment. It is essential for health care practitioners to be knowledgeable about nerve agents, potential antidotes, and the predeployment stockpiles that exist. Atropine, pralidoxime, and diazepam are agents that all play a critical role in the treatment of patients in this clinical scenario. The dosing of these agents and the clinical monitoring parameters of therapy are unique in this situation, further complicating patient management. The management of these patients following an event will necessitate the coordinated effort of all health care practitioners, regardless of discipline, and will involve the systematic application of each institution's emergency preparedness plan to help ensure the safe and effective utilization of antidotal therapy.

REFERENCES

Abdollahi, M., & Karami-Mohajeri, S. (2012). A comprehensive review on experimental and clinical findings in intermediate syndrome caused by organophosphate poisoning. *Toxicology and Applied Pharmacology*, *258*(3), 309–314.

Agency for Toxic Substances and Disease Registry. (2011). *Medical Management Guidelines for Nerve Agents: Tabun (GA); Sarin (GB); Soman (GD); and VX*. Retrieved July 29, 2013, from http://www.atsdr.cdc.gov/MHMI/mmg166.pdf

Anderson, P. D. (2012). Emergency management of chemical weapons injuries. *Journal of Pharmacy Practice*, *25*(1), 61–68.

Bajgar, J. (2004). Organophosphates/nerve agent poisoning: Mechanism of action, diagnosis, prophylaxis, and treatment. *Advances in Clinical Chemistry*, *38*, 151–216.

Barthold, C. L., & Schier, J. G. (2005). Organic phosphorus compounds–nerve agents. *Critical Care Clinics*, *21*(4), 673–689, v-vi.

Berry, W. K., & Davies, D. R. (1970). The use of carbamates and atropine in the protection of animals against poisoning by 1,2,2-trimethyl propyl methylphosphonofluoridate. *Biochemical Pharmacology*, *19*(3), 927–934.

Bevan, D. R., Donati, F., & Kopman, A. F. (1992). Reversal of neuromuscular blockade. *Anesthesiology*, *77*(4), 785–805.

Bird, S. B., Gaspari, R. J., & Dickson, E. W. (2003). Early death due to severe organophosphate poisoning is a centrally mediated process. *Academic Emergency Medicine*, *10*(4), 295–298.

Carpentier, P., Delamanche, I. S., Le Bert, M., Blanchet, G., & Bouchaud, C. (1990). Seizure-related opening of the blood-brain barrier induced by soman: Possible correlation with the acute neuropathology observed in poisoned rats. *Neurotoxicology*, *11*(3), 493–508.

Collombet, J. M. (2011). Nerve agent intoxication: Recent neuropathophysiological findings and subsequent impact on medical management prospects. *Toxicology and Applied Pharmacology*, *255*(3), 229–241.

Dunn, M. A., & Sidell, F. R. (1989). Progress in medical defense against nerve agents. *Journal of the American Medical Association*, *262*(5), 649–652.

Eddleston, M., Dawson, A., Karalliedde, L., Dissanayake, W., Hittarage, A., Azher, S., . . . Buckley, N. A. (2004). Early management after self-poisoning with an organophosphorus or carbamate pesticide—a treatment protocol for junior doctors. *Critical Care*, *8*(6), R391–R397.

Grange-Messent, V., Bouchaud, C., Jamme, M., Lallement, G., Foquin, A., & Carpentier, P. (1999). Seizure-related opening of the blood-brain barrier produced by the anticholinesterase compound, soman: New ultrastructural observations. *Cellular and Molecular Biology*, *45*(1), 1–14.

Grob, D., & Harvey, J. C. (1958). Effects in man of the anticholinesterase compound sarin (isopropyl methyl phosphorofluoridate). *Journal of Clinical Investigation*, *37*(3), 350–368.

Jokanovic, M. (2009). Medical treatment of acute poisoning with organophosphorus and carbamate pesticides. *Toxicology Letters*, *190*(2), 107–115.

Keeler, J. R., Hurst, C. G., & Dunn, M. A. (1991). Pyridostigmine used as a nerve agent pretreatment under wartime conditions. *Journal of the American Medical Association*, *266*(5), 693–695.

Lallement, G., Dorandeu, F., Filliat, P., Carpentier, P., Baille, V., & Blanchet, G. (1998). Medical management of organophosphate-induced seizures. *Journal of Physiology Paris*, *92*(5–6), 369–373.

Leadbeater, L., Inns, R. H., & Rylands, J. M. (1985). Treatment of poisoning by soman. *Fundamental and Applied Toxicology*, *5*(6 Pt. 2), S225–S231.

Lee, E. C. (2003). Clinical manifestations of sarin nerve gas exposure. *Journal of the American Medical Association*, *290*(5), 659–662.

Levinson, D. R. (2009). *CDC's CHEMPACK project: Nerve agent antidote storage*. (OEI-04-08-00040). Office of Inspector General. Retrieved from http://oig.hhs.gov/oei/reports/oei-04-08-00040.pdf

Maggi, L., & Mantegazza, R. (2011). Treatment of myasthenia gravis: Focus on pyridostigmine. *Clinical Drug Investigation*, *31*(10), 691–701.

Mason, H. J., Waine, E., Stevenson, A., & Wilson, H. K. (1993). Aging and spontaneous reactivation of human plasma cholinesterase activity after inhibition by organophosphorus pesticides. *Human and Experimental Toxicology*, *12*(6), 497–503.

Masson, P., & Goasdoue, J. L. (1986). Evidence that the conformational stability of 'aged' organophosphate-inhibited cholinesterase is altered. *Biochimica et Biophysica Acta*, *869*(3), 304–313.

McDonough, J. H., Jr., McLeod, C. G., Jr., & Nipwoda, M. T. (1987). Direct microinjection of soman or VX into the amygdala produces repetitive limbic convulsions and neuropathology. *Brain Research*, *435*(1–2), 123–137.

McDonough, J. H., Jr., & Shih, T. M. (1997). Neuropharmacological mechanisms of nerve agent-induced seizure and neuropathology. *Neuroscience and Biobehavioral Reviews*, *21*(5), 559–579.

Medicis, J. J., Stork, C. M., Howland, M. A., Hoffman, R. S., & Goldfrank, L. R. (1996). Pharmacokinetics following a loading plus a continuous infusion of pralidoxime compared with the traditional short infusion regimen in human volunteers. *Journal of Toxicology-Clinical Toxicology*, *34*(3), 289–295.

Murray, D. B., Eddleston, M., Thomas, S., Jefferson, R. D., Thompson, A., Dunn, M., . . . Blain, P. G. (2012). Rapid and complete bioavailability of antidotes for organophosphorus nerve agent and cyanide poisoning in minipigs after intraosseous administration. *Annals of Emergency Medicine*, *60*(4), 424–430.

Mutch, E., Blain, P. G., & Williams, F. M. (1992). Interindividual variations in enzymes controlling organophosphate toxicity in man. *Human and Experimental Toxicology*, *11*(2), 109–116.

Namba, T., Nolte, C. T., Jackrel, J., & Grob, D. (1971). Poisoning due to organophosphate insecticides. Acute and chronic manifestations. *American Journal of Medicine*, *50*(4), 475–492.

Newmark, J. (2004). Nerve agents: Pathophysiology and treatment of poisoning. *Seminars in Neurology*, *24*(2), 185–196.

Nozaki, H., Hori, S., Shinozawa, Y., Fujishima, S., Takuma, K., Sagoh, M., . . . Aikawa, N. (1995). Secondary exposure of medical staff to sarin vapor in the emergency room. *Intensive Care Medicine*, *21*(12), 1032–1035.

Okudera, H. (2002). Clinical features on nerve gas terrorism in Matsumoto. *Journal of Clinical Neuroscience*, *9*(1), 17–21.

Okumura, T., Takasu, N., Ishimatsu, S., Miyanoki, S., Mitsuhashi, A., Kumada, K., . . . Hinohara, S. (1996). Report on 640 victims of the Tokyo subway sarin

attack. *Annals of Emergency Medicine*, *28*(2), 129–135.

Rickett, D. L., Glenn, J. F., & Beers, E. T. (1986). Central respiratory effects versus neuromuscular actions of nerve agents. *Neurotoxicology*, *7*(1), 225–236.

Schexnayder, S., James, L. P., Kearns, G. L., & Farrar, H. C. (1998). The pharmacokinetics of continuous infusion pralidoxime in children with organophosphate poisoning. *Journal of Toxicology-Clinical Toxicology*, *36*(6), 549–555.

Selden, B. S., & Curry, S. C. (1987). Prolonged succinylcholine-induced paralysis in organophosphate insecticide poisoning. *Annals of Emergency Medicine*, *16*(2), 215–217.

Senanayake, N., & Karalliedde, L. (1987). Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. *New England Journal of Medicine*, *316*(13), 761–763.

Sener, E. B., Ustun, E., Kocamanoglu, S., & Tur, A. (2002). Prolonged apnea following succinylcholine administration in undiagnosed acute organophosphate poisoning. *Acta Anaesthesiology Scandinavica*, *46*(8), 1046–1048.

Sidell, F. R., & Borak, J. (1992). Chemical warfare agents: II. Nerve agents. *Annals of Emergency Medicine*, *21*(7), 865–871.

Sudakin, D. L., Mullins, M. E., Horowitz, B. Z., Abshier, V., & Letzig, L. (2000). Intermediate syndrome after malathion ingestion despite continuous infusion of pralidoxime. *Journal of Toxicology-Clinical Toxicology*, *38*(1), 47–50.

Thiermann, H., Steinritz, D., Worek, F., Radtke, M., Eyer, P., Eyer, F., . . . Zilker, T. (2011). Atropine maintenance dosage in patients with severe organophosphate pesticide poisoning. *Toxicology Letters*, *206*(1), 77–83.